Introduction of bromine and chlorine substituents in medium ring ethers and lactones

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A convenient preparation of α-halo enamines using oxalyl halides is described together with applications of these reagents in the halogenation of β-hydroxy cyclic ethers and lactones.

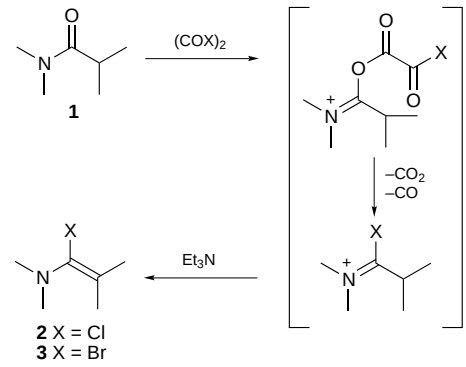
There has recently been considerable interest in the synthesis of medium ring ether marine natural prducts, and significant progress has been achieved both in ring expansion reactions and in the controlled cyclisation of acyclic precursors.[1] Of all the features present in the various *Laurencia* and related cyclic ether metabolites which have been isolated from red algae the β-halo ether substituent is probably the most challenging. In connection with our own studies towards the synthesis of medium ring marine natural products[2–4] we required a method for the stereospecific introduction of chlorine and bromine β to the ring oxygen. The most common way to achieve this so far has been displacement of hydroxy group using a phosphorus activating reagent,[5] a xanthate,[6] or a metal-mediated epoxide opening.[7] Alternatively, the halogen can be present before ring closure as in the radical cyclisations employed by Lee.[8] The β-ring oxygen can suppress nucleophilic displacement of a leaving group substantially,[9] and can potentially promote oxonium ion formation and rearrangement.[10] Here we report the use of α-halo enamine reagents to effect halide introduction by substitution reactions.

An α-halo enamine reagent was initially introduced by Speziale,[11] who prepared *N*,*N*-diethyltrichlorovinylamine and showed subsequently that it could be used to transform alcohols into alkyl chlorides with stereochemical inversion.[12] The more reactive 1-chloro-*N*,*N*,2-trimethylpropenamine **2** was later developed by Ghosez[13,14] who demonstrated conversion of carboxylic acids into acid halides.[15] We subsequently used this reagent for the first time with allylic alcohols and showed that it could be used to introduce an allylic chloro substituent into the side chain of the *cis*-maneonenes isolated from *Laurencia nidifica*.[16] Further examples have subsequently been reported by Ghosez to prepare simple alkyl halides,[17] and there are examples of steroid halogenation in the patent literature.[18] Despite having the advantage that they can be used under essentially neutral conditions these reagents have received little attention from organic chemists, possibly owing to the need to use liquid phosgene to prepare the α-chloro enamine **2**, and a subsequent bromide displacement reaction to convert **2** into the α-bromo enamine **3**.[14] In the present work, it has been found that the amide **1** reacts with oxalyl chloride or oxalyl bromide followed by treatment with triethylamine to furnish the respective α-halo enamines **2** and **3**† (Scheme 1).

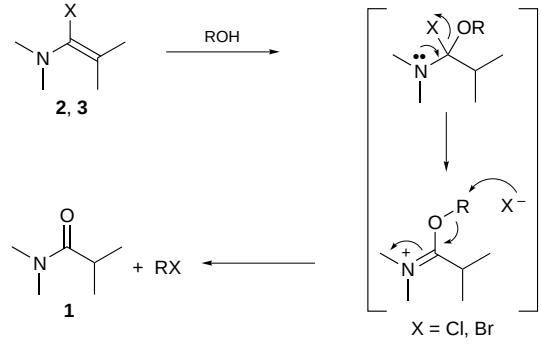
The reagents **2** and **3** smoothly converted alcohols into alkyl halides in CH_2Cl_2 at room temperature (Scheme 2). The displacement was shown to take place with inversion of configuration as illustrated (Table 1, entry 1) for the conversion of (−)-menthol into (+)-neomenthyl halides.[17] A trace of alkene elimination product (*ca.* 5%) was also detected. This could be suppressed by performing the reactions at −78 °C.

The successful halogenation of β-hydroxy cyclic ethers was initially demonstrated (Table 1, entry 2) using 3-hydroxytetrahydrofuran. β-Hydroxy 9- and 10-membered lactones[19] were halogenated readily, and the stereochemical inversion was confirmed by comparison of the ^{1}H NMR difference NOE spectra of **13** and **15**.‡ In the chloro compound **15** a large (11%) NOE was observed between the signals due to H-8 (δ 4.46, dt, *J* 9, 4, 4 Hz) and H-9 (δ 4.95–5.05, m), but no NOE was observed between the signals due to H-8 and H-9 in the alcohol **13**. The hydroxy-substituted 8-membered lactones **19**[20] and 9-membered cyclic ethers **21**[4] proved more problematical, and underwent either isobutyryl esterification or decomposition, resulting in low yields of halides. By changing the solvent to a mixture (1 : 1) of propylene oxide and CH_2Cl_2 the decomposition was suppressed, although the reaction rate was much slower, and the reaction was generally conducted at room temperature. Incorporation of dried 4 Å molecular sieves prevented esterification.§ The reaction was also used to prepare the (*E*)-pentenynyl bromide **25** from the alcohol **24**, which gave poor yields of bromide using other methods (Table 1, entry 8).

In summary, an exceptionally mild method of preparing the α-halo enamine reagents **2** and **3** has been described. These versatile reagents are effective in converting hydroxy compounds into the corresponding halo compounds under mild conditions, even under circumstances where rate suppression occurs due to the β-oxygen effect. Applications in the synthesis of halogenated medium ring ether natural products can be expected to follow.

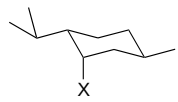
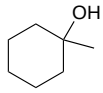
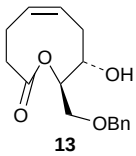
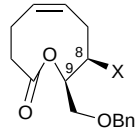
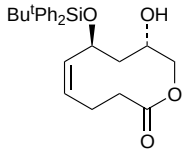
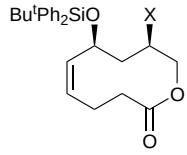
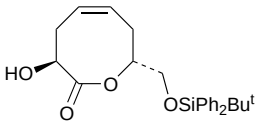
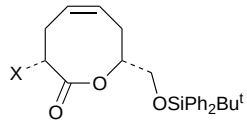
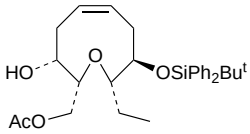
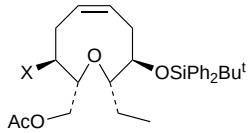
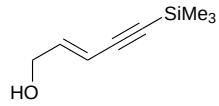
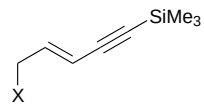


Scheme 1



Scheme 2

Table 1 Halogenation of alcohols using α-halo enamines

Entry	Alcohol	Alkyl halide
1	 **4**	 **5** X = Br 97%[a] **6** X = Cl 84%
2	 **7**	 **8** X = Br 70% **9** X = Cl 56%
3	 **10**	 **11** X = Br 67% **12** X = Cl 0%
4	 **13**	 **14** X = Br 78% **15** X = Cl 81%
5	 **16**	 **17** X = Br 72% **18** X = Cl 86%
6	 **19**	 **20** X = Br 42%[b]
7	 **21**	 **22** X = Br 45%[c] **23** X = Cl 71%
8	 **24**	 **25** X = Br 72%

[a] See footnote ¶. [b] 38% starting material recovered; [c] 54% starting material recovered.

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Footnotes

† Preparation of α-bromo enamine **3** from oxalyl bromide. A solution of freshly distilled *N*,*N*,2-trimethylpropionamide **1** (5.0 g, 43 mmol) in dry CH_2Cl_2 (10 cm³) was added dropwise over 20 min to a cooled (0 °C), mechanically stirred solution of oxalyl bromide (10.0 g, 46 mmol) in dry CH_2Cl_2 (10 cm³), producing mild effervescence. The mixture was stirred for 2 h and was then cooled further (−78 °C). Freshly distilled dry Et_3N (7.0 cm³, 50 mmol) was added dropwise to the white paste over 10 min. The mixture was warmed to room temperature, stirred for 2 h, and then filtered and distilled under vacuum to give 1-bromo-*N*,*N*,2-trimethylpropenamine **3** as a clear, moisture-sensitive liquid (4.3 g, 55%), bp 44 °C at 10 mmHg, ρ^{20} 1.20 (Found: C, 40.1; H, 7.1; N, 7.9. $C_6H_{12}BrN$ requires C, 40.5; H, 6.8; N, 7.9%); ν_{max}(neat)/cm^{-1} 1654, 1450, 1298, 1124, 1011, 803; δ_H(400 MHz, $CDCl_3$) 1.77 (6H, s, CMe_2), 2.28 (6H, s, NMe_2); δ_C(100 MHz, $CDCl_3$) 21.6 (CMe_2), 43.7 (NMe_2), 126.0 (C-2), 140.4 (C-1).

‡ All new compounds provided satisfactory spectroscopic (^{1}H and ^{13}C NMR, IR, MS) and microanalytical or high resolution MS data.

§ Representative procedure for the preparation of the bromo compound **22**. Dried 4 Å molecular sieves (100 mg) were added to a stirred solution of the alcohol **21**[4] (17 mg, 34 μmol) in CH_2Cl_2 (0.3 cm³) and propylene oxide (0.3 cm³) under nitrogen, which after 10 min was cooled (−78 °C). α-Bromo enamine **3** (0.05 cm³) was added and the mixture was warmed to ambient temperature and left overnight. MeOH (0.05 cm³) was added and the mixture was chromatographed on silica gel (hexanes–diethyl ether) to give the bromide **22** (8 mg, 45%) and starting material **21** (9 mg, 54%).

¶ $[\alpha]_D$ + 73 (*c* 0.83, EtOH) [lit.,[21] +59 and +58 (*c* 1.38 and 1.44 in EtOH)]. NMR data were identical to those reported.[22]

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